

REMARKS

Claims 1-6, 9, 11-15, 17-20, and 22 are pending in the instant application. Applicants acknowledge with appreciation that the Examiner has withdrawn the rejections of claims 1-6, 9, 11-15, 17-20, and 22-26 under 35 U.S.C. § 112, first paragraph, scope of enablement, and the rejections of claims 1, 12, 15, and 24 under 35 U.S.C. § 112, second paragraph, and that claims 1-6, 9, 15, 17-20, and 22 are allowed. By this amendment, claims 11-15 have been amended and new claims 28 and 29 have been added. In particular, claim 11 has been amended to indicate that the method is directed to protection of neuronal tissue from injury or tissue damage “during a surgical procedure.” In addition, the term “in need thereof” has been added to clarify that the “mammal” is at risk for injury or tissue damage during a surgical procedure. The term “wherein the EPO is administered prior to a medical or surgical procedure” has been deleted. Support for amended claim 11 may be found in the specification at p. 5, l. 34 to p. 6, l. 2; p. 14, ll. 15-16; and p. 19, ll. 5-18, especially ll. 16-18. Claim 12 has been amended to delete the phrase “at least one time 4 hours to 24 hours” and to delete the term “medical” procedure. Support for amended claim 12 may be found in the specification, *e.g.*, at p. 5, l. 34 to p. 6, l. 2; p. 8, l. 19; p. 14, ll. 12-16 and ll. 22-24; p. 19, ll. 16-18; p. 28, ll. 19-22; Example 4, starting at p. 32; Example 5, starting at p. 33; and Example 6 at p. 34. Claim 13 has been amended to present the claim as an independent claim. Support for amended claim 13 may be found in the specification, *e.g.*, at p. 14, ll. 5-8, ll. 10-12, and ll. 24-26. Claim 14 has been amended to delete the term “coronary artery bypass procedure.” New claims 28 and 29, directed to “a coronary artery bypass procedure” and “the use of a heart-lung machine,” respectively, have been added to more particularly point out and distinctly claim the invention. Support for new claims 28 and 29 may be found in the specification, *e.g.*, at p. 14, ll. 15-16 and Example 6 at p. 34, particularly ll. 6-9.

As such, no new matter has been added with this amendment. Therefore, claims 1-6, 9, 11-15, 17-20, 22, 28, and 29 will be pending upon entry of the instant amendment.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION (NEW MATTER) SHOULD BE WITHDRAWN

The Examiner states at pages 2-5 of the Office Action that claims 11-14 fail to comply with the written description requirement and are new matter. The first paragraph of 35 U.S.C. § 112 requires that the specification convey that the inventor had possession of the claimed subject matter. *Ralston Purina Co. v. Far-Mar-Co.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). To satisfy this written description requirement, the specification need not provide *in haec verba* support for the claimed subject matter. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Applicants respectfully submit that claims 11-14, as amended, and new claim 28, are supported by the written description of the specification, for the reasons discussed below.

By this amendment, claim 11 has been amended to recite a method for protecting neuronal tissue from injury or tissue damage during a surgical procedure to a mammal in need thereof, and to remove the phrase “wherein EPO is administered prior to a medical or surgical procedure.” Support for this amendment may be found in the specification at page 5, line 34 to page 6, line 2; page 14, lines 15-16; and page 19, lines 5-18, especially lines 16-18.

Additionally, claim 12 has been amended to recite a method for protecting neuronal tissue from injury or tissue damage during a surgical procedure, wherein the EPO is administered prior to surgery. Support for this amendment can be found throughout the specification, as follows. At page 5, lines 34 to page 6, line 2, the specification states that “EPO may be used to prevent injury or tissue damage during surgical procedures” (emphasis added). Reading this, one of skill in the art would understand that, to prevent injury or tissue damage, EPO is administered prior to the surgery. The disclosure of using EPO in prophylactic treatments similarly would be understood by the skilled artisan to mean administering EPO prior to the injury or damage (see, *e.g.*, p. 8, l. 19). The specification, in reference to the types of disorders that occur during surgical procedures, discloses that “[a]cute and early treatment of these disorders may be carried out . . . such that treatment may be started as soon as suspicion of potential neurologic damage is ascertained.” (See specification at p. 14, ll. 12-16 and ll. 22-24.) Moreover, the specification further states at page 19, lines 16-16, that “EPO may be administered to prevent injury or tissue damage resulting from risk of injury or tissue damage during surgical procedures” (emphasis added).

In addition, the working examples of the invention disclosed in the specification provide “standard, universally-accepted tests in animal models predictive of prophylactic and therapeutic benefit” (see p. 28, ll. 19-22). Examples 4, 5, and 6 demonstrate that EPO administered prior to a surgically-induced injury prevents the injury and resultant tissue damage, such as the injury and tissue damage that can occur during surgery. Of particular relevance to protecting neuronal tissue from injury or tissue damage during a surgical procedure, the specification discloses an animal model of myocardial ischemia (see Example 6 at p. 34). In this example, a surgery is performed that is analogous to coronary artery bypass surgery in human patients. First, EPO was administered to rats, and then, 24 hours later, the rats were anesthetized and placed on assisted ventilation, a thoracotomy was performed, and the left anterior descending coronary artery was reversibly sutured (see ll. 6-9). These steps parallel those performed during coronary artery bypass procedures in humans, as exemplified in Calafiore *et al.* (1996, “Left Anterior Descending Coronary Artery Grafting via Left Anterior Small Thoracotomy Without Cardiopulmonary Bypass,” *Ann Thorac Surg* 61:1658-65 (Exhibit A; “Calafiore”)), which describes a surgery involving a thoracotomy wherein the left anterior descending coronary artery is sutured. (See Abstract; p. 1658, left column, 3rd paragraph; and p. 1659, left column, 2nd paragraph to right column, 2nd full paragraph). For additional animal models predictive of protecting neuronal tissue from injury or tissue damage during a surgical procedure, see Example 4, starting at page 32, wherein EPO is administered 24 hours before, at time of, and up to 6 hours after injury by surgically induced stroke, and Example 5, starting at page 33, wherein EPO administered 24 hours before, at time of, and up to 3 hours after blunt trauma injury.

Claim 13 is amended and presented as an independent claim directed to the protection of neuronal tissue from injury or tissue damage during labor or childbirth. Support for this amendment may be found in the specification, *e.g.*, at p. 14, ll. 5-8 and 10-12, and in particular, the statement that EPO can be administered “before or during labor” (p. 14, ll. 24-26).

Finally, claim 14 has been amended to delete the reference to “coronary artery bypass procedure.” The deleted subject matter has been presented in new claim 28. Examples of coronary artery bypass procedures taught in the specification include surgery in which a heart-lung machine is used (see, *e.g.*, p. 14, ll. 15-16) and Example 6 at p. 34, which teaches

an animal model of surgically-induced ischemia through coronary artery occlusion that parallels the steps of coronary artery bypass surgery in the clinic (see discussion with respect to Example 6 and Calafiore in the paragraph at p. 8, above). Support for new claim 29, directed to "the use of a heart-lung machine," may be found in the specification, *e.g.*, at p. 14, ll. 15-16.

Therefore, for all the reasons discussed above, the disclosure provides sufficient written description support, including working examples of art-accepted animal models, for claims 11-14 as amended and new claims 28 and 29. In view of the foregoing amendments and arguments, applicants submit that the rejections of claims 11-14 for written description (new matter) under 35 U.S.C. §112, first paragraph, have been overcome and/or obviated and should be withdrawn.

CONCLUSION

Entry of the foregoing remarks and amendment into the record of the above-identified application is respectfully requested. Applicants estimate that the remarks and amendments made herein now place the pending claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Please charge any required fee to Jones Day Deposit Account No. 50-3013. A duplicate of this sheet is enclosed for accounting purposes.

Date:	<u>December 17, 2007</u>	Respectfully submitted,	
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Enclosures



Express Mail No.: EV 544 896 488 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Brines et al.

Confirmation No.: 6595

Application No.: 09/716,960

Group Art Unit: 1647

Filed: November 21, 2000

Examiner: DeBerry, Regina M.

For: METHODS FOR TREATMENT OF
NEURODEGENERATIVE CONDITIONS BY
PERIPHERALLY ADMINISTERED
ERYTHROPOIETIN

Attorney Docket No.: 10165-009-999

AMENDMENT FEE TRANSMITTAL SHEET

Mail Stop After Final
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Sir:

The fee required to be filed with the accompanying amendment of even date herewith concerning the above-identified application has been estimated to be \$0.00.

The claim amendment fee has been estimated as shown below:

(Col. 1)			(Col. 2)		(Col. 3)		SMALL ENTITY		OTHER THAN A SMALL ENTITY	
CLAIMS REMAINING AFTER AMENDMENT			HIGHEST NO. PREVIOUSLY PAID		PRESENT EXTRA		RATE	ADDIT. FEE	OR	ADDIT. FEE
TOTAL	19	MINUS	25				x 25	\$		x 50
INDEP.	4	MINUS	4				x 105	\$		x 210
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM								\$		\$
							TOTAL	\$	OR	TOTAL
										\$ 0.00

However, should any fee be required for filing the accompanying amendment, please charge the required fee to Jones Day Deposit Account No. 50-3013. A copy of this sheet is enclosed.

Respectfully submitted,

Date: December 17, 2007

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Enclosure

Left Anterior Descending Coronary Artery Grafting via Left Anterior Small Thoracotomy Without Cardiopulmonary Bypass

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Background. We explored the possibility of anastomosing the left internal mammary artery (LIMA) to the left anterior descending artery in a beating heart via a left anterior small thoracotomy.

Methods. This procedure was performed in 155 of 162 scheduled patients; in 7 (4.3%) the left anterior descending artery was not suitable or was too small. The chest was opened in the fourth intercostal space (mean wound length, 10.5 cm) and the LIMA was harvested for about 4 cm. The left anterior descending artery was occluded by means of two 4/0 Prolene (Ethicon, Somerville, NJ) sutures, and the proximal suture was snared. The anastomosis was performed with two 8/0 Prolene sutures while the heart was beating. Early postoperatively all patients underwent repeat angiography or a Doppler flow assessment of the LIMA or both.

Results. The LIMA was connected directly to the left anterior descending artery in 144 patients and with

interposition of an inferior epigastric artery in 11. In 2 patients the diagonal branch was also grafted using an inferior epigastric artery from the LIMA. One patient (0.6%) died 38 days after the operation due to multiorgan failure. Nine patients (5.8%) had failure requiring a redo operation: 7 (4.5%) early and 2 (1.3%) late. One additional patient had a late percutaneous transluminal coronary angioplasty for anastomotic stenosis. At a mean 5.6 months of follow-up, 143 patients (92.2%) were alive, asymptomatic with or without medical treatment, and without cardiac events.

Conclusions. Left internal mammary artery-to-left anterior descending artery anastomosis performed on a beating heart via a left anterior small thoracotomy is a safe procedure. In selected patients the operation has good early and midterm results.

(*Ann Thorac Surg* 1996;61:1658-65)

Coronary artery bypass grafting without cardiopulmonary bypass (CPB) via a median sternotomy is a well-established procedure, extensively used by some surgical teams [1-4]. The use of a left thoracotomy to graft one or more coronary arteries was the first approach to myocardial revascularization [5] and is today widely used in redo operations [6].

Recently some authors proposed the use of a left minithoracotomy or a left mediastinotomy to perform an anastomosis between the left internal mammary artery (LIMA) and the left anterior descending coronary artery (LAD), on a beating heart [7, 8], with the aid of a thoracoscope [9, 10], or with the support of femorofemoral bypass [11].

In November 1994 we began our experience with LAD grafting on a beating heart via a left anterior small thoracotomy (LAST). Herein we report the midterm results of patients who underwent this procedure.

Material and Methods

From November 1994 to December 1995, 155 of 162 scheduled patients underwent LIMA-to-LAD anastomosis via a LAST performed on a beating heart. The procedures were performed by 3 surgeons (A.M.C., G.D.G., G.T.). Preoperative data of these patients are shown in Table 1.

Surgical Indications

Candidates were patients with isolated LAD disease in whom a percutaneous transluminal coronary angioplasty was not advisable (proximal or complex stenoses), not successful, or not possible (occluded LAD); patients with LAD disease and a second vessel (right coronary or circumflex arteries) occluded and recanalized or with a mild stenosis or stenosis that could be dilated; patients with LAD disease and disease of two other vessels with a combination of the situations previously described; and patients with multiple vessel disease in whom CPB had a presumed high morbidity (cancer, severe renal failure, diffuse cerebrovascular disease, diffuse peripheral vasculopathy, severe respiratory insufficiency, old age).

Presented at the Thirty-second Annual Meeting of The Society of Thoracic Surgeons, Orlando, FL, Jan 29-31, 1996.

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Table 1. Preoperative Data (155 Patients)

Variable	Value
Age (y)	60.9 ± 9.6 (38-81) ^a
≥70	26 (16.7%)
≤50	30 (19.3%)
Sex (female)	17 (10.9%)
Unstable angina	68 (43.8%)
Previous MI	60 (38.7%)
Risk factors	
Renal failure	8 (5.1%)
Cancer	3 (1.9%)
Diffuse encephalopathy	8 (5.1%)
Diffuse vasculopathy	4 (2.6%)
Untouchable aorta	2 (1.3%)
Redo	5 (3.2%)
Coronary lesions	
LAD disease	
isolated	78 (50.3%)
+ RCA or + Cx	50 (32.2%)
+ RCA + Cx	27 (17.4%)
LM	4 (2.6%)
EF	
Mean	0.61 ± 0.13 (0.15-0.88) ^a
≤0.35	6 (3.8%)

^a Range.

Cx = circumflex artery; EF = ejection fraction; LAD = left anterior descending; LM = left main; MI = myocardial infarction; RCA = right coronary artery.

Anatomic Indications

At angiography the distal LAD must be at least 1.5 mm and not be calcified. An intramyocardial vessel, often detectable at angiography, is, of course, an absolute contraindication for this procedure. The anastomotic site is 2 to 4 cm below the second diagonal branch; this is the segment that must be carefully evaluated.

Surgical Technique

Anesthesia is induced with fentanyl and sodium thiopental and is maintained with fentanyl and droperidol. Muscular relaxation was obtained with pancuronium bromide. A Carlens tube was used in the beginning of our experience to avoid left lung ventilation if necessary, but its use has now been discontinued. In the final part of the operation a mixture of N₂O and O₂ is used to allow rapid awaking of the patient.

The chest is opened via a LAST in the fourth intercostal space (sometimes in the fifth); the pleural cavity is opened routinely. The ribs are retracted and the pericardium is incised vertically (parallel to the sternum). The LAD is inspected and the feasibility of the operation is explored. An intramyocardial, calcified, or small LAD makes the anastomosis impossible. As well, an LAD located beneath the sternum is a contraindication to operation. When one of these possibilities occurs, the chest is closed and the sternal approach is used.

If the LAD is abnormally lateral, the inferior epigastric artery is used to lengthen the LAD. In our experience we

used 13 inferior epigastric arteries, ten to extend the LIMA end-to-end, one as a side branch of an in situ LIMA to reach the LAD, and two as a side branch of an LIMA to an LAD to graft an important diagonal branch. The surgical technique was previously reported by us [12].

The LIMA is harvested for a short length (4 to 5 cm), upward to the superior intercostal space and downward to the level of the inferior rib. The LIMA is harvested skeletonized in the great majority of the cases to have more length. After systemic heparinization (1 mg/kg), the LIMA is injected with 3 mL of a solution containing papaverine (1 mg/mL of saline solution) and is distally clipped [12].

The LAD is then occluded proximally and distally using a 4/0 Prolene (Ethicon, Somerville, NJ) suture with a 25-mm needle passed twice to surround the vessel. To avoid any direct compression of the suture on the coronary wall [10], the needle, after the first bite, is passed through a small piece of silicone tubing. The proximal 4/0 suture is gently snared to ensure an operative field as bloodless as possible (Fig 1).

The distal LIMA is prepared as usual. The anastomotic site of the LAD is dissected. To reduce movements of the artery, four to six Prolene 4/0 radial sutures are passed through the fat surrounding the LAD on both sides and fixed to the edges of the wound. This technical procedure stabilizes the artery, making the anastomosis easier (see Fig 1).

The LAD is then incised with a knife (Sharp point 15-degree) for 4 to 5 mm. The anastomosis is performed using two sutures of 8/0 Prolene with a 6- or 8-mm needle. Both of them are passed three times at the heel and at the apex; the LIMA is then pulled down to reach the LAD. The two edges of the vessels now face each other, and the anastomosis is completed with two running sutures from both sides.

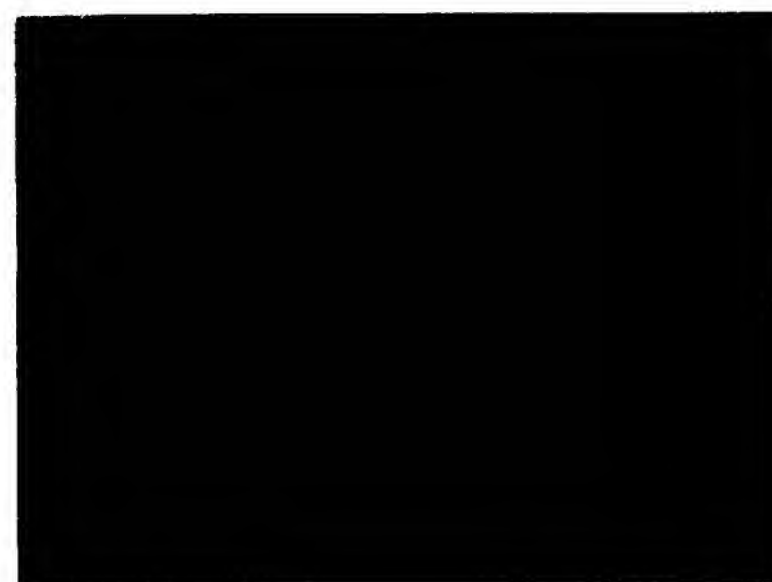


Fig 1. The left anterior descending artery is occluded proximally and distally by means of two 4/0 Prolene sutures with the interposition of a small piece of a silicone tubing to avoid any direct compression of the artery. The proximal suture is snared. Five stay sutures are passed around the left anterior descending artery to reduce its movements.

The LIMA and the LAD are unclamped and hemostasis is carefully checked. A drain is positioned in the left pleural cavity together with a small catheter to infuse an analgesic drug (bupivacaine). The wound is closed as usual.

Postoperative Course

All patients were admitted to the intensive care unit, where blood samples, chest roentgenograms, and electrocardiogram were obtained. The flow pattern in the LIMA was assessed by continuous-wave Doppler echocardiography. As the LIMA remains in its natural position for three intercostal spaces, the flow pattern is easily detectable. The appearance of diastolic flow is considered a demonstration of patency of the anastomosis. This flow pattern is compared with that of the unused right internal mammary artery, the flow of which is mainly systolic (Fig 2).

A few hours later the patients were transferred to the ward where, in the evening and twice on the first postoperative day, flow evaluation of the LIMA was repeated. The drain and the intrapleural catheter were removed on the morning of the first postoperative day. In the first part of our experience angiography was scheduled for every patient in the first days after the operation; recently this examination has been performed only in the presence of a doubtful or negative flow Doppler evaluation, as the sensitivity and specificity of the Doppler flow evaluation were found to be 100%. On the morning of the second postoperative day the great majority of the patients were discharged home.

Follow-up

All patients were followed up at our outpatient clinic at the end of the first and the sixth postoperative months. All patients performed a stress test and, if possible, myocardial scintigraphy was performed at the time of the first and the second visit, respectively. Doppler flow evaluation was also repeated.

The follow-up was 100% complete; it ranged from 15 days to 13 months (mean, 5.5 months).

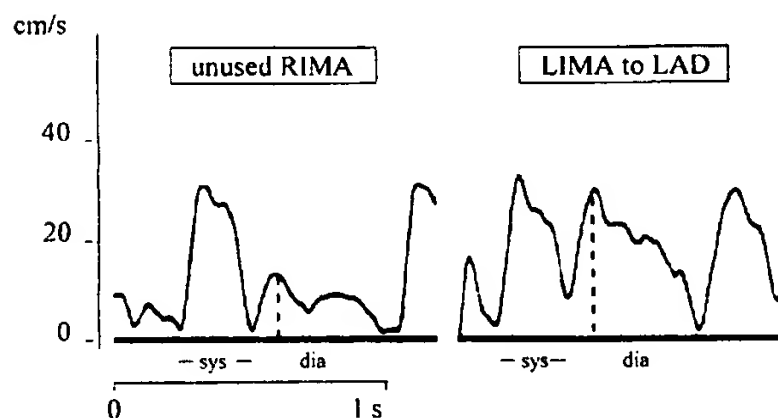


Fig 2. Postoperative continuous-wave Doppler assessment. In the unused right internal mammary artery (RIMA) the flow is mainly systolic (sys). When the left mammary artery (LIMA) is connected to the left anterior descending (LAD) artery a wide diastolic component (dia) appears, due to the peculiar characteristic of the coronary bed.

Table 2. Clinical Results (155 Patients)

Variable	Value
Wound length (cm)	10.5 ± 1.2
Operative time (h)	2.0 ± 0.7
LAD occlusion time (min)	23.3 ± 5.8 (16-39) ^a
Anastomotic time (min)	15.2 ± 4.2 (9-28) ^a
Surgical technique	
LIMA to LAD	142 (91.6%)
LIMA + IEA to LAD	10 (6.5%)
IEA from LIMA to LAD	1 (0.6%)
LIMA to LAD and IEA from LIMA to D	2 (1.3%)
ICU stay (h)	4.2 ± 5.6 (1-23) ^a
Bleeding (mL/12 h)	84.3 ± 134.3 (20-570) ^a
Transfused patients	2 (1.3%)
Redo for bleeding	2 (1.3%)
Death	1 (0.6%)
Early redo	7 (4.5%)
Late redo	2 (1.3%)
Late PTCA	1 (0.6%)

^a Range.

D = diagonal branch; ICU = intensive care unit; IEA = inferior epigastric artery; LAD = left anterior descending; LIMA = left internal mammary artery; PTCA = percutaneous transluminal coronary angioplasty.

Results

Clinical results are summarized in Table 2. In 7 patients (4.3%) the LAD was not found or considered to be too small. The chest was closed and all patients underwent LIMA-to-LAD grafting via a median sternotomy, with (5) or without (2) cardiopulmonary bypass. In all cases but 1 the LAD was occluded and was not completely visualized in the preoperative angiography; in the remaining patient the angiography was not correctly considered.

The other 155 patients underwent LIMA to LAD anastomosis without CPB via LAST. Technical details are shown in Table 2. Thirty-two patients were extubated in the operating room; 77 of the remaining patients were extubated during the first hour and all the others in the first 3 hours after intensive care unit admission.

One patient died 38 days after the operation. He was a 65-year-old man with chronic renal failure, left internal carotid artery stenosis, and occlusion of the right internal carotid artery and the left common and external iliac arteries. He underwent left carotid endarterectomy, femorofemoral grafting and LIMA-to-LAD anastomosis via LAST. After an initial uneventful postoperative course, he was reoperated on for massive bleeding from the chest drain. At reoperation a branch of the LIMA was bleeding. Acute anemia caused deterioration of his pulmonary and renal function. He died in multiorgan failure.

Two additional patients were reoperated on for bleeding after 12 and 14 hours; an intercostal artery from the LIMA and from the chest wall were the respective causes of the hemorrhage. Interestingly, both arteries appeared longer than at the moment when the chest was closed the first time.



Fig 3. Angiography shows the anastomosis between the left internal mammary artery and the left anterior descending artery. Only the distal portion of the left internal mammary artery was dissected to reach the anastomotic site.

All patients had one or more flow Doppler evaluations, and 53 of them had early postoperative angiography (1-26 days) (Fig 3).

The early success (normal angiography or wide diastolic flow at Doppler evaluation) rate was 95.5% (148/155); it was 98% (49/50) in the last part of our experience. Seven patients (4.5%) underwent reoperation during the same hospitalization; the cause of early failure was occluded distal LIMA in 5 cases, kinking of the LIMA against the sternum in 1 patient, and kinking of an inferior epigastric artery from the LIMA to the LAD in the remaining patient. All were reoperated on via median sternotomy. The LAD was always patent and the LIMA was reused in all patients. In 2 patients additional grafts were added to the other occluded coronary vessels.

The mean postoperative hospital stay was 53 ± 28 hours; this value concerns 147 patients (the patient who died and the 7 patients reoperated on in the same hospitalization were excluded). Seventy-seven percent of our patients were discharged on the second postoperative day. Longer hospitalization was mainly due to routine repeat angiography.

All patients had pulsatile wave color Doppler evaluation of the LIMA. As the basal assessment shows only that the anastomosis is patent, in 21 patients we studied the flow in the LIMA after a stress test to investigate how much flow passed through the anastomosis. We found that the diastolic flow velocity increases the lower the resistance to the flow is (Figs 4, 5). We also studied in 7 patients during angiography, by means of an intracoronary Doppler probe, the possibility of the LIMA to increase acutely diastolic flow after adenosine-induced myocardial hyperemia. All patients showed a physiologic

increase in the ratio between basal and induced flow (>2.5). These data clearly emphasize that persistence of LIMA collaterals does not adversely affect the diastolic flow toward the LAD.

Four patients (2.5%) had late angiography (1 to 7 months) for recurrent symptoms: angina in 3 and persisting effort dyspnea in 1. This latter patient showed a patent anastomosis but persisting anterolateral dyskinesia, more localized than on the preoperative angiography. The remaining 3 patients showed stenosis at the proximal (2) or distal (1) portions of the LIMA-to-LAD anastomosis. One of them had successful percutaneous transluminal coronary angioplasty of the proximal LAD (protected by the LIMA), and 2 underwent redo operation via a conventional median sternotomy.

At follow-up, 143 patients (92.2%) are alive and free of symptoms without a cardiac event. Stress test and myocardial scintigraphy showed no ischemia in any patient. Patients with multiple-vessel disease continue to receive medical treatment.

Comment

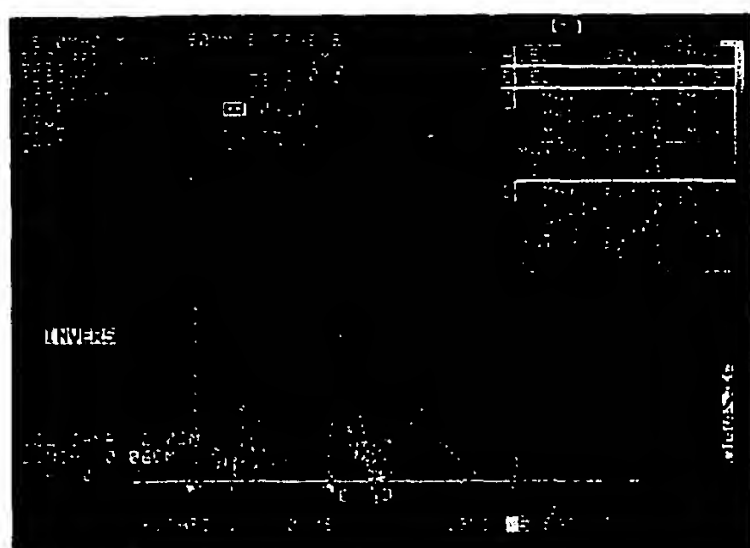
Coronary artery bypass grafting without CPB via a median sternotomy is a technical solution to be considered in every patient in whom CPB is associated with increased morbidity and the anatomy is favorable. An LIMA-to-LAD anastomosis in a beating heart via a LAST is a different approach to the surgical treatment of coronary heart disease for different reasons.

Surgical invasiveness is minimal and the patient's comfort is high; furthermore, postoperative hospital stay can be limited to 2 days. We think that this aspect of the LAST operation is due to avoidance of CPB and not due to the position or length of the incision. Other authors [11] are using other routes, using femorofemoral bypass and inducing cold ventricular fibrillation. Patency of the anastomosis can be immediately assessed and flow reserve can be checked noninvasively at any moment. At the end of the procedure, the patient has a patent LIMA on the LAD, which is, to the best of our knowledge, the most important factor for long-term survival after surgical myocardial revascularization [13]. Moreover, pericardial adhesions are mild and the mediastinum is untouched; therefore, redo coronary artery bypass grafting actually becomes the first operation.

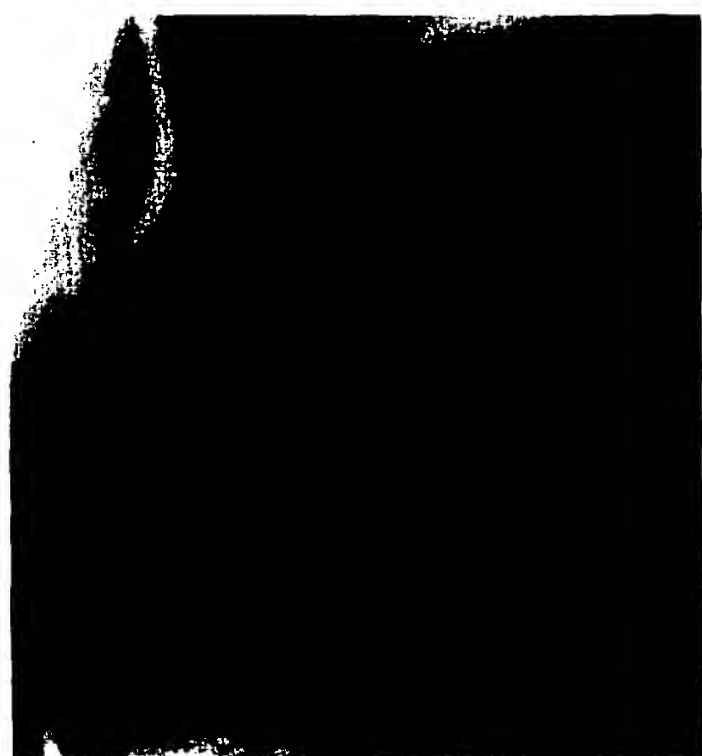
However, some concerns exist regarding the LAST operation:

Left Anterior Descending Artery Occlusion

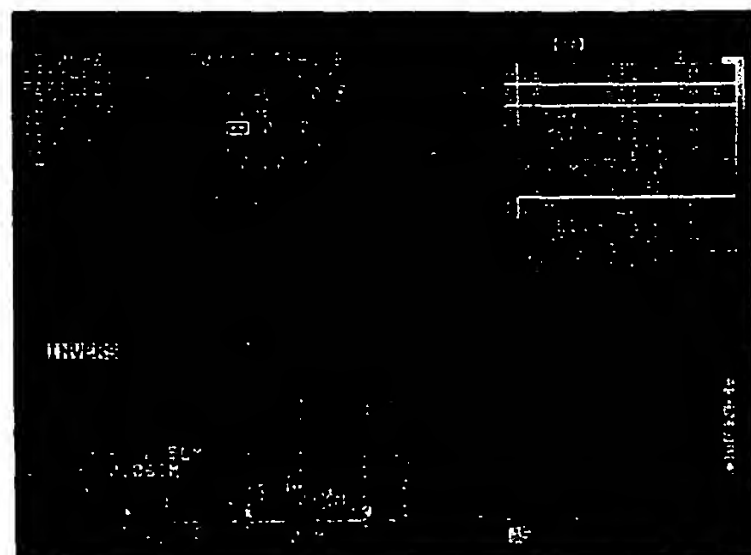
In our experience occlusion of the distal LAD never caused hemodynamic changes or rhythm disturbances. These findings must be emphasized as the LAST does not give the possibility of rapid cannulation of the patient. Nevertheless our policy (the LAD is occluded before preparation of the LIMA and stabilization of the coronary vessel) makes the anastomotic time safe, as the arteriotomy is made several minutes (7 to 10 minutes) after the occlusion.



A

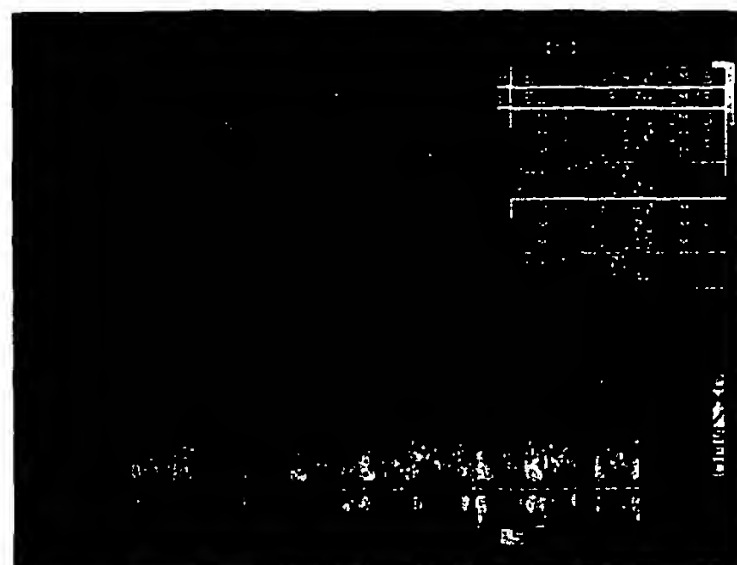


B



C

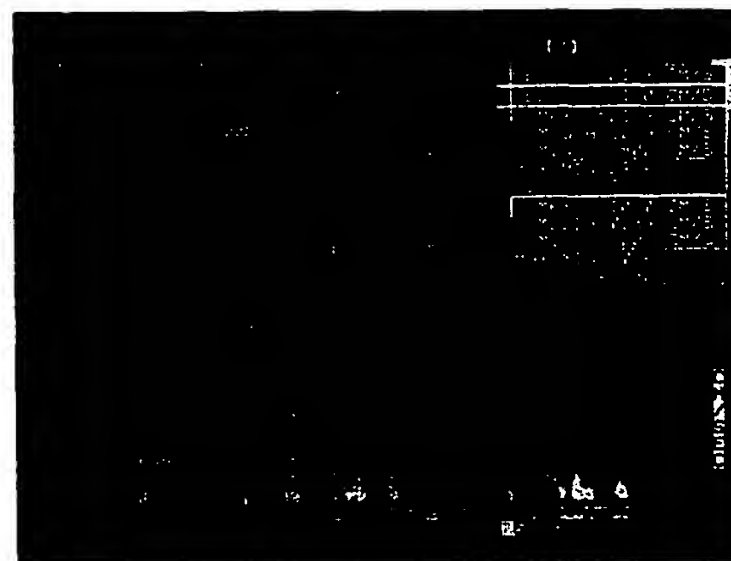
Fig 4. (A) Basal flow evaluation in a left internal mammary artery connected to a left anterior descending artery in a patient with a patent anastomosis at angiography (B) and normal left ventricular function (0.73). After a stress test, the diastolic flow velocity increased from 13.4 to 22.8 cm/s (+71.0%) (C).



A



B



C

Fig 5. (A) Basal flow evaluation in a left internal mammary artery connected to a left anterior descending artery in a patient with a patent anastomosis at angiography (B) but with a reduced ejection fraction (0.45) due to a previous anterior myocardial infarction. After a stress test, the diastolic velocity increased from 8.57 to 10.7 cm/s (+24.8%) (C).

Technical Feasibility

The LIMA-to-LAD anastomosis is easier via LAST than via a median sternotomy. In fact, the heart in the latter situation rotates with every beat, as the pericardium is opened and the lungs are displaced. Via LAST the heart moves up and down, as the pericardium and the left lung remain in place. Fixation of the LAD is easier to obtain by pulling the artery upward, in the direction of its physiologic movement, by means of radial stitches. Furthermore, the LAD moves toward the surgeon, whereas via median sternotomy, the artery moves away from the surgeon. Finally, the use of two sutures to perform the anastomosis stabilizes the operative field. The LAST operation was not possible in only 4.3% of scheduled patients, and never for technical reasons. With increasing experience this value decreased to 2.0% (1/50) and may be reduced further.

Left Internal Mammary Artery Collaterals

As the LIMA is left in place for about three intercostal spaces, the intercostal, muscular, and sternal collaterals are not occluded as usual. The hemodynamic importance of this anatomic situation is controversial. We know that flow in collaterals occurs in systole, whereas flow in the LAD is diastolic; there is no competition between the different territories if the total amount of flow is sufficient. We have evidence, from our previous experience [12, 14], that the LIMA can carry enough blood for more than one myocardial territory. Others [15] have shown that the LIMA can provide blood to the whole heart. This is clearly shown by negative stress tests and myocardial scintigraphies. Moreover, the flow mapping performed in some of our patients showed a physiologic increase of flow to the LAD after adenosine-induced myocardial hyperemia, demonstrating the limited hemodynamic importance of persistent collaterals.

Cause of Graft Failure

We think that a good anastomotic technique is crucial for the success of this procedure. However, we realize that skeletonized LIMA is able to lengthen in the early postoperative period: in 1 of our patients the cause of early graft occlusion was kinking of a skeletonized LIMA against the sternum. This is an isolated case, but this observation needs further study. In our experience the causes of the graft failure were mainly in the LIMA, with the exception of patients with late anastomotic stenosis. However, as with any new technique, a learning curve is expected and increasing experience has allowed us to have only one graft failure in the last 50 patients.

Conclusion

An LIMA-to-LAD anastomosis in a beating heart via LAST is a different approach to the treatment of coronary artery disease. Its interest, if surgical indications were limited to patients with isolated LAD disease in whom percutaneous transluminal coronary angioplasty is not possible or was unsuccessful, would be only technical. However, we think that the LAST operation can be

extended to patients with multiple-vessel disease with a combination of occlusion or mild or peripheral stenoses of coronary vessels different from the LAD. As we know, the natural history of patients with one- or two-vessel disease, but with a patent LAD, is favorable. A palliative operation that gives a patent LIMA-to-LAD graft with low risk and high success rate must be considered in some patients, especially in high-risk subgroups. In fact, reduction of postoperative morbidity and consequent shorter postoperative hospital stay are very important end points in a period when cost containment is crucial in any healthcare system.

Our early results allow us to state that the LAST operation is safe and reproducible. We believe that this operation will have its place among the techniques of myocardial revascularization, although we recognize that longer follow-up and experience are needed.

References

1. Benetti FJ, Naselli G, Wood M, Geffner L. Direct myocardial revascularization without extracorporeal circulation. Experience in 700 patients. *Chest* 1991;100:312-6.
2. Buffolo E, Silva de Andrade JC, Rodrigues Branco JN, et al. Coronary artery bypass surgery without cardiopulmonary bypass. *Ann Thorac Surg* 1996;61:63-6.
3. Pfister AJ, Zaki MS, Garcia JM, et al. Coronary artery bypass without cardiopulmonary bypass. *Ann Thorac Surg* 1992;54:1085-92.
4. Fanning WJ, Kakos GS, Williams TE Jr. Reoperative coronary bypass grafting without cardiopulmonary bypass. *Ann Thorac Surg* 1993;55:486-9.
5. Kolesov VI. Mammary artery-coronary artery anastomosis as method of treatment for angina pectoris. *J Thorac Cardiovasc Surg* 1967;54:535-44.
6. Suma H, Kigawa I, Horii T, Tanaka J, Fukuda S, Wanibuchi Y. Coronary artery reoperation through the left thoracotomy with hypothermic circulatory arrest. *Ann Thorac Surg* 1995;60:1063-6.
7. Subramanian V, Stelzer P. Clinical experience with minimally invasive coronary artery bypass grafting (CABG). *Eur J Cardiothorac Surg* (in press).
8. Standbridge R De L, Symons GV, Banwell PE. Minimal access surgery for coronary artery revascularization. *Lancet* 1995;346:837.
9. Benetti FJ, Ballester C, Sani G, Doonstra P, Grandjean J. Video assisted coronary artery bypass surgery. *J Cardiac Surg* 1995;10:620-5.
10. Acuff TE, Landreneau RJ, Griffith BP, Mack MJ. Minimally invasive coronary artery bypass grafting. *Ann Thorac Surg* 1996;61:135-7.
11. Robinson MC, Gross DR, Zeman W, Stedje-Larsen E. Minimally invasive coronary artery bypass grafting. A new method using an anterior mediastinotomy. *J Cardiac Surg* 1995;10:529-26.
12. Calafiore AM, Di Giammarco G, Luciani N, et al. Composite arterial conduits for a wider myocardial revascularization. *Ann Thorac Surg* 1994;58:185-90.
13. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal mammary artery graft on 10 year survival and other cardiac events. *N Engl J Med* 1986;314:1-6.
14. Calafiore AM, Di Giammarco G, Teodori G, et al. Radial artery and inferior epigastric artery in composite grafts: improved midterm angiographic results. *Ann Thorac Surg* 1995;60:517-24.
15. Tector AJ, Amundsen S, Schmahl TM, Kress DC, Peter M. Total revascularization with T grafts. *Ann Thorac Surg* 1994;57:33-9.

DISCUSSION

DR ROBERT W. EMERY (Minneapolis, MN): Doctor Calafiore, I congratulate you, your co-investigators, and your colleagues who are bringing us back to the future. We, at the Minneapolis Hearts Institute, began a program of minimally invasive bypass operations 6 months ago and have completed single- or double-vessel procedures in 25 patients via left anterior thoracotomy, right anterior thoracotomy, or a ministernotomy with results comparable with yours. I have found the operation to be easier on the patients but more difficult for the surgeon.

Because of some concern around construction of the anastomosis, we have documented anastomotic patency in the operative field using a thermal imaging camera (OPGAL, Jerusalem, Israel). The camera is directed to the anterior surface of the heart, a large black area gently cooled with topical iced saline solution around the distribution of the LAD after removal of the distal occluding clip on the LAD. The serrafine clip on the mammary artery, and the proximal LAD occluder are in place.

After release of the LIMA occluder, a white streak in the middle of the field demonstrates warm blood flowing from the internal mammary artery into the cooled heart, assuring intraoperatively the patency of the anastomosis. This has offered us confidence in an aggressive approach to continue this program.

Your pioneering efforts are greatly appreciated.

DR CALAFIORE: Thank you very much.

DR LAWRENCE I. BONCHEK (Lancaster, PA): I too congratulate Dr Calafiore and associates on their innovative and superior results. My colleagues and I have been interested in this procedure, but before initiating an approach that inevitably involves certain compromises, we thought it important to review our experience with conventional isolated internal mammary artery grafting of the LAD.

Since 1983 we have had experience with 168 patients. Importantly, 16% were operated on emergently for percutaneous transluminal coronary angioplasty failure (of a total of 35 patients who had emergency operation). Elective operation was performed in only 21% of the patients. The postoperative length of stay in 1995, which reflects the recent trend toward shorter hospital discharge and is much more relevant than our earlier experience, was 4.4 days. The average hospital cost for elective patients in 1995, which I consider comparable with the type of patient who would undergo this procedure, was \$8,300. There were no deaths and no strokes. The rate of reoperation for bleeding was 1%. One deep sternal infection and two perioperative infarctions occurred, and only 5 patients needed inotropic support at any time postoperatively.

I want to emphasize that these results are not presented in the spirit of controversy; rather, we hope that these results will be a useful benchmark against which to compare less invasive operations. We would not wish to compromise the long-term results of an operation that has proved to be the best that we can do, namely, conventional internal mammary artery to the LAD, merely for the sake of convenience.

I have two questions, among many others that I could ask. We know that even small thoracotomies can cause chronic pain. What has been your experience in this regard?

Second, what is your approach to patients who have a stenosis in a high diagonal branch of the LAD that may be out of your surgical field? Is there a temptation to minimize such lesions to avoid a sternotomy?

DR CALAFIORE: In our series we had no patient with chronic pain; however, the number of patients is not sufficient to generalize.

In a patient with a stenosis of an important diagonal branch, we perform a median sternotomy; the LAST operation is not suitable for all the patients. But, if possible, a percutaneous transluminal coronary angioplasty of the diagonal branch after a successful LIMA-LAD anastomosis can be scheduled. This staged approach was done in our institution in some selected cases with good results. Furthermore, this can be a good point of meeting with cardiologists.

DR LEONARDO LIMA (Paris, France): I congratulate Dr Calafiore on his excellent paper. I would like to make a few comments and ask several questions.

My colleagues and I had a patient who was operated on using the same technique and who in fact could not be discharged from the intensive care unit as he continued to have angina. A repeat angiogram showed no anastomotic stenosis and no supraclavicular stenosis. However, a large collateral branch issuing from the LIMA was confirmed by Doppler to be the origin of a steal syndrome. He was discharged in good health after a second intervention, during which the collaterals were ligated.

In La Pitie Hospital (Paris), along with Dr Nataf and Prof Gandjbakhch, we have used another approach to this particular kind of patient. In our opinion, it is important to harvest the LIMA by a thoracoscopic approach as this method produces a mammary artery of just the correct length, with no kinking and no steal syndrome. It is not a difficult technique, only requiring 20 minutes. The thoracotomy required is minimal (4 cm) and the bypass graft can be carried out on the beating heart without cardiopulmonary bypass.

In certain cases, we consider myocardial protection to be essential. This is achieved by means of an intracoronary shunt. We have operated on 14 patients using these techniques with good results in all cases.

I have two questions. First of all, in your series you state that 10% of your patients do not have a mammary artery of sufficient length and in these cases you have performed a LIMA-epigastric artery anastomosis before epigastric-LAD anastomosis. Do you think that the epigastric artery will provide the same long-term results as the LIMA?

Second, kinking seems to be a problem in this kind of patient. How may it best be avoided?

DR CALAFIORE: The mammary artery in some patients is not enough long to reach a very lateral LAD. As we routinely use inferior epigastric artery for coronary artery bypass grafting, it is very easy for us to harvest this conduit to lengthen the mammary artery. We think that this is an easy and safe technique to reach the LAD in every position. For this reason I am not concerned about the length of the mammary artery.

Kinking of the mammary artery was, of course, one of the steps in our learning curve. With increasing experience, we can modulate the length of the LIMA according to the LAD position.

No patients in this series had a steal syndrome. Even if some anecdotal cases are reported, the steal syndrome is not a real problem.

DR VALAVANUR A. SUBRAMANIAN (New York, NY): I congratulate Professor Calafiore for superb clinical results of a large series of this operation in a very short time. When my

colleagues and I introduced this operation in April 1994 we had one concept in our mind; this is a different operation than the traditional midline sternotomy off-pump cardiopulmonary bypass. In fact, the first operation I did off pump was a minithoracotomy bypass.

When we performed a midline sternotomy incision for conventional coronary bypass, it occurred to us that we were perhaps approaching the left coronary system from a wrong incision, because the left side of the coronary arterial system is on the left side of the chest. Therefore, the anterior portion of the pericardium and the mediastinal structures in the anterior thoracotomy are preserved as the heart is much closer to the surface and the anastomosis is easier. I still have concern regarding the wider population of surgeons who are going to embark on this operation. The two important technical points of this operation are the length of the mammary artery and the actual meticulous performance of the anastomosis on a beating heart. We believe that it is important to have enough length of the mammary artery, and we have been excising the fourth costal cartilage routinely. I have one question to Dr Calafiore: You had an 8.3% incidence of inferior epigastric artery use. Is it because of the too laterally placed LAD or is it because the length of the mammary artery is not enough in that incision?

The second point is, how can we make the anastomosis in this operation more comfortable and easier to do so that it could be applied widely to the cardiac surgical community? We are working on several ways to immobilize the coronary artery. A mechanical stabilization platform, as proposed by the Utrecht group, is one direction we are currently assessing. We are also looking at some pharmacologic maneuvers to stop the heart momentarily to place the key heel and toe sutures in the LAD. I do not think that there is going to be a tremendous amount of evolution of this part of the operation to make this safer for most of the cardiac surgeons. Until we do that, this operation is going to continue to be limited to a few technical experts.

DR CALAFIORE: The necessity to elongate the LIMA with an inferior epigastric artery was due to a lateral LAD.

DR SUBRAMANIAN: Do you have any suggestion to slow the heart rate or make it so perfect that we can do the anastomosis easier? Raising the comfort level of the anastomosis is very important for this operation to be widely practiced.

DR CALAFIORE: I agree with you.

DR FEDERICO BENETTI (Santa Fe, Argentina): I congratulate Dr Calafiore for the nice presentation. I have only two com-

ments. First, we prefer to go more lateral. There is a direct relationship between using the scope and the length of the incision in our experience. Also, we prefer to take all of the length of the mammary artery and clip all the branches because we need to reproduce the same situation that you have with the sternotomy. If we have a good immediate patency rate, we assume that is the same situation in normal coronary operations in the long term.

Second, I think that it is very important for the average surgeon to train, to do some cases by a sternotomy without a pump. I notice in this period of time that the surgeons who have been trained before without a pump perform the procedure more comfortably.

DR NOEL L. MILLS (New Orleans, LA): I might just make a short comment. I think we are all very interested in this technique. It has drawn a lot of interest, and we're looking at it carefully. I think we have to be careful not to abdicate our responsibility of performing a complete revascularization with this procedure, thereby urging the cardiologist to do more angioplasties on vessels that can be reached by this approach. Issues of cost containment should not dictate what may not be best for our patients in the long run.

DR CARY W. AKINS (Boston, MA): In cardiac surgery and, indeed, in angioplasty incomplete revascularization has been clearly identified as a main contributor to higher hospital morbidity and mortality and long-term complication rates. If you are going to make the argument that this can be applied as a "culprit lesion" approach to people with multiple vessel disease, it seems to me that you need longer follow-up. Second, if you have a significant amount of anastomotic irregularities, which seemed to me in one group to be about 10%, if you are going to focus your operation on the LAD, then the LAD operation has to be done right.

DR CALAFIORE: No, it is not 10%. It is 4%.

DR AKINS: In one group that was followed up by both echocardiography and angiography, you have documented this.

DR CALAFIORE: In the early postoperative period we follow up the patients only with Doppler flow evaluation. We reserve angiography only to those cases where the Doppler echocardiography shows only a systolic pattern or doubtful flow. The percentage of occluded anastomoses in this group is higher because of selection of patients.